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<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 7/48</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/19665</b> <b>(43) International Publication Date:</b> 14 May 1998 (14.05.98)
<b>(21) International Application Number:</b> PCT/US96/17522 <b>(22) International Filing Date:</b> 4 November 1996 (04.11.96) <b>(71) Applicant (for all designated States except US):</b> THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KAWATO, Junji [JP/JP]; 15-9 Nakamura-cho, Omihachiman, Shiga 523 (JP). VENKATESWARAN, Ananthanarayan [IN/JP]; 4-127-904, Koyo-cho, Naka 1-chome, Higashinada-ku, Kobe 658 (JP). <b>(74) Agents:</b> REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SKIN LIGHTENING COMPOSITIONS  <b>(57) Abstract</b>  Disclosed is a skin lightening cosmetic composition comprising: a) a safe and effective amount of at least one water-soluble reducing agent selected from the group consisting of sodium sulfite, potassium sulfite, sodium hydrogen sulfite, potassium hydrogen sulfite, sodium metabisulfite, potassium metabisulfite, ammonium sulfite, ammonium hydrogen sulfite, formic acid, oxalic acid and mixtures thereof and, b) cosmetically acceptable carrier for the water-soluble reducing agent wherein the composition is substantially free of hydroquinone or its derivatives. Also disclosed is a method for skin lightening in mammals comprising topically applying to the skin said skin lightening cosmetic composition.		

## SKIN LIGHTENING COMPOSITIONS

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TECHNICAL FIELD

The present invention relates to the field of skin lightening. Specifically, the present invention relates to novel compositions comprising a specific reducing agent for skin lightening.

BACKGROUND

10 The formation of melanin depends upon the availability of three substances: (1) a suitable substrate such as tyrosine and dopa, (2) molecular oxygen and (3) enzyme tyrosinase (a copper protein complex). If any of these substances are absent or reduced, the formation of melanin is impaired.

The reducing agent retards melanin formation by the following three mechanism:

15 (1) It sequesters some of the copper in the enzyme system and the enzymatic formation of melanin is reduced by sequestering copper since the co-enzyme of tyrosinase is a copper protein complex. (2) The necessary substrates for melanin formation (tyrosine and dopa) are formed from both bacteriological and enzymatic breakdown of protein. A decrease in the available bacteria would depress proteolytic destruction and thereby aid in decreasing melanogenesis since the reducing agent such as sodium sulfite is a bactericide. (3) The strong reducing agent such as  
20 sodium sulfite itself gets oxidized in preference to the melanin substrates.

Romanian patent application No. 100161 is assigned to Institute of Chemical-Pharmaceutical Research, Bucharest and discloses that a reducing agent such as sodium metabisulfite is used to eliminate the unpleasant odor.

25 USP4136166 is assigned to Helena Rubinstein, USP4792443 is assigned to Warner-Lambert, USP5514437 is assigned to The Proctor & Gamble Company and Japanese Patent Laid-open No.6-263624 is assigned to Mochida Pharmaceutical Co. and they disclose that sulfite salts, hydrogen sulfite salts and metabisulfite salts are used as a stabilizer or an antioxidant.

30 Japanese Patent Laid-open No.54-129134 is assigned to Shiseido and discloses that a combination of (i) sulfite or hydrogensulfite and organic solvent, (ii) ferrous salt and (iii) hydrogen peroxide shows an effect of bleaching a melanin of hair

Japanese Patent Laid-open No. 3-101609 is assigned to Sansyo Pharmaceutical, No.3-279313 is assigned to Shiseido, No. 4-352708 is assigned to Kose, No. 63-174910 is assigned to Shiseido and No.7-25742 is assigned to Kao, and they disclose that sulfites, hydrogensulfites and pyrosulfites have an effect of preventing the product from coloring.

Japanese Patent Laid-open No.5-139928 is assigned to Hisamitsu Pharmaceutical Co. and discloses that sodium hydrogen sulfite and sodium metabisulfite are used as an antioxidant.

Japanese Patent Laid-open No. 5-179300 is assigned to Kitano Kagaku and discloses that sodium hydrogen sulfite is used to bleach leather.

5 Japanese Patent Laid-open Nos. 7-215888, 8-12548, 8-12549, 8-12550, 8-12552, 8-12554, 8-12556, 8-12557, 8-12558 and 8-12565 are assigned to Shiseido and Japanese Patent Laid-open No. 59-157009 is assigned to Yakurigaku Cyuo kenkyusho and they disclose that very low level of sodium hydrogensulfite or sodium sulfite is included in a skin lightening or melanin controlling composition comprising a specific skin lightening or melanin controlling active ingredient.

10 It has been discovered that the water-soluble reducing agent selected from the group consisting of sodium sulfite, potassium sulfite, ammonium sulfite, sodium hydrogen sulfite, potassium hydrogen sulfite, ammonium hydrogen sulfite, sodium metabisulfite, potassium metabisulfite, formic acid and oxalic acid, and mixtures thereof lightens mammalian skin.

#### 15 SUMMARY

The present invention relates to skin lightening cosmetic compositions comprising:

- 20 a) a safe and effective amount of at least one water-soluble reducing agent selected from the group consisting of sodium sulfite, potassium sulfite, ammonium sulfite, sodium hydrogen sulfite, potassium hydrogen sulfite, ammonium hydrogen sulfite, sodium metabisulfite, potassium metabisulfite, formic acid, oxalic acid, and mixtures thereof
- b) a cosmetically acceptable carrier for the water-soluble reducing agent wherein said compositions are substantially free of hydroquinone or its derivatives.

The skin lightening compositions of the present invention preferably comprise said water-soluble reducing agent and lecithin.

25 The skin lightening compositions of the present invention more preferably comprise (a) said water-soluble reducing agent, (b) a cosmetically acceptable liquid oil, (c) a polyhydric alcohol, (d) a solid fatty alcohol, (e) surfactant, (f) water and (g) lecithin, wherein at least a portion of the above components (a), (b), (c), (d), (e), (f) and (g) forms a liquid crystal.

30 Such compositions satisfy the need for skin lightening effect of mammalian skin

#### DETAILED DESCRIPTION

As used herein, "topical application" means directly laying on or spreading on outer skin.

As used herein, "skin lightening" means decreasing melanin in skin, including one or more of overall lightening of basal skin tone, lightening of hyperpigmented lesions including age

spots, melasma, chloasma, freckles, post inflammatory hyperpigmentation or sun-induced pigmented blemishes.

As used herein, "solid" means solid form at the temperature of 25 °C, and "liquid" means liquid form at the temperature of 25 °C.

5 As used herein, all percentages are by weight unless otherwise specified.

A. Water-soluble reducing agent

10 The composition of the present invention comprises a water-soluble reducing agent. The reducing agent is selected from the group consisting of sodium sulfite, potassium sulfite, ammonium sulfite, sodium hydrogen sulfite, potassium hydrogen sulfite, ammonium hydrogen sulfite, sodium metabisulfite, potassium metabisulfite, formic acid, oxalic acid, and mixtures thereof. If the composition comprises more than about 5% by weight of the composition, of the reducing agent, it will cause safety issue, and if it comprises less than 0.1% by weight of the composition, of the reducing agent, enough skin lightening effect is not expected.

15 The skin lightening composition of the present invention comprises preferably from about 0.1% to about 5%, more preferably from about 0.15% to about 5%, still more preferably from about 0.2% to about 5%, most preferably from about 0.25% to about 5% by weight of the composition, of the reducing agent.

In the reducing agent, sodium sulfite, sodium hydrogen sulfite, sodium metabisulfite and the mixtures thereof are preferred.

20 The skin lightening composition of the present invention is substantially free of hydroquinone or its derivatives, and preferably hydroquinone and its derivatives are absent from the present invention as they are thought to disturb the lightening activity of the water-soluble reducing agent. Such hydroquinone derivatives include 4-[(tetrahydro-2H-pyran-2-yl)oxy]phenol and 4-[(tetrahydro-2H-thiopyran-2-yl)oxy]phenol and ones which are described in  
25 WO 9523780 which is hereby incorporated by reference.

B. Lecithin

30 The skin lightening composition of the present invention preferably comprises said water-soluble reducing agent and lecithin. Lecithin is a natural product derived from soybean or egg yolk, and used for enhancing the skin lightening effect of the reducing agent. If the composition comprises more than 10% by weight of the composition, of lecithin, it will cause tackiness problem, and if it comprises less than 0.01% by weight of the composition, of lecithin, enough enhancing effect of the skin lightening effect of the reducing agent is not expected.

35 The lecithin level in the skin lightening composition of the present invention is preferably from about 0.01% to about 10 %, more preferably from about 0.5% to about 3% by weight of the composition.

### C. Cosmetically Acceptable Carrier

The phrase "cosmetically acceptable carrier", as used herein, means one or more compatible solid or liquid fillers, diluents, extenders and the like, which are cosmetically acceptable as defined herein. The term "compatible", as used herein, means that the components of the compositions of this invention are capable of being comingled with the primary actives of the present invention, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. The type of carrier utilized in the present invention depends on the type of product desired. The topical compositions useful in the present invention may be made into a wide variety of product types. These include, but are not limited to, lotions, creams, gels, sticks, sprays, ointments, pastes, mousses and cosmetics (e.g., solid, semi-solid, liquid make-up, including foundations). These product types may comprise several types of carriers including, but not limited to solutions, aerosols, emulsions (including water-in-oil and oil-in-water), gels, solids, and liposomes.

Solutions according to the present invention typically include water and cosmetically acceptable organic solvent. Water is a preferred solvent. Examples of suitable organic solvents include: propylene glycol, polyethylene glycol (e.g., Molecular Weight 200-600 g/mole), polypropylene glycol (e.g., Molecular Weight 425-2025 g/mole), glycerol, 1,2,4-butanetriol, 1,2,6-hexanetriol, ethanol, isopropanol, sorbitol esters, butanediol, and mixtures thereof. Solutions useful in the present invention preferably contain from about 50% to about 99.9% of water or both water and an acceptable organic solvent, and the water-soluble reducing agent in the above described amounts.

Aerosols according to the present invention can be formed by adding a propellant to a solution such as described above. Exemplary propellants include chloro-fluorinated lower molecular weight hydrocarbons. Additional propellants that are useful herein are described in Sagarin, Cosmetics Science and Technology, 2nd Edition, Vol. 2, pp. 443-465 (1972), incorporated herein by reference. Aerosols are typically applied to the skin as a spray-on product.

Emulsions according to the present invention generally contain a solution as described above and a lipid or oil. Lipids and oils may be derived from animals, plants, or petroleum and may be natural or synthetic (i.e., man-made). Preferred emulsions also contain a humectant, such as glycerin. Emulsions will preferably further contain from about 1% to about 10%, more preferably from about 2% to about 5%, of an emulsifier, based on the weight of the carrier. Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Patent 3,755,560, issued August 28, 1973, Dickert et al.; U.S. Patent 4,421,769,

issued December 20, 1983, Dixon et al.; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324 (1986), each incorporated herein by reference.

The emulsion may also contain an anti-foaming agent to minimize foaming upon application to the skin. Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use.

The emulsions preferably comprise a silicone for imparting a preferred skin feel. Generally such silicones have a low molecular weight. Suitable silicones include cyclomethicones, dimethicones and blends having cyclomethicones, dimethicones and/or dimethiconol, such as Dow Corning 200 fluid (especially 10 cs) and Dow Corning Q2-1401. Such silicones are commercially available from the Dow Corning Corp. of Midland, MI.

The topical compositions of the present invention may comprise a topical cosmetically acceptable emollient. Such compositions preferably contain from about 2% to about 50% of the emollient. As used herein, "emollient" refers to a material used for the prevention or relief of dryness, as well as for the protection of the skin. A wide variety of suitable emollients are known and may be used herein. Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 32-43 (1972), incorporated herein by reference, contains numerous examples of materials suitable as an emollient.

Lotions and creams according to the present invention generally comprise a solution carrier system and one or more emollients. Lotions typically comprise from about 0.01% to about 50%, preferably from about 0.1% to about 20%, of emollient; from about 30% to about 99%, preferably from about 50% to about 90% of water; and the primary actives in the above described amounts. A cream typically comprises from about 5% to about 50%, preferably from about 10% to about 30%, of emollient; from about 45% to about 90%, preferably from about 50% to about 85% of water; and the primary actives in the above described amounts.

#### D. Formation of a liquid crystal

The skin lightening composition of the present invention more preferably comprises (a) said water-soluble reducing agent, (b) a cosmetically acceptable liquid oil, (c) a polyhydric alcohol, (d) a solid fatty alcohol, (e) surfactant, (f) water and (g) lecithin, wherein at least a portion of the above components (a), (b), (c), (d), (e), (f) and (g) forms a liquid crystal.

The liquid crystal can be detected by observing the shape of the liquid crystal by a polarization microscope.

The level of the cosmetically acceptable liquid oil in the skin lightening composition of the present invention comprising the liquid crystal is preferably from about 1% to about 50%, more preferably from about 3% to about 25% by weight of the composition.

The level of the polyhydric alcohol in the skin lightening composition of the present invention comprising the liquid crystal is preferably from about 0.1% to about 20%, more preferably from about 1% to about 10% by weight of the composition.

5 The level of the solid fatty alcohol in the skin lightening composition of the present invention comprising the liquid crystal is preferably from about 0.1% to about 20%, more preferably from about 1.0% to about 5% by weight of the composition.

The level of the surfactant in the skin lightening composition of the present invention comprising the liquid crystal is preferably from about 0.1% to about 10%, more preferably from about 0.1% to about 3% by weight of the composition.

10 The level of the water in the skin lightening composition of the present invention comprising the liquid crystal should be preferably from about 40% to about 90%, more preferably from about 60% to about 90% by weight of the composition.

The level of the lecithin in the skin lightening composition of the present invention comprising the liquid crystal is preferably from about 0.01% to about 10%, more preferably from about 0.1% to about 3% by weight of the composition.

15 The skin lightening composition of the present invention comprising the liquid crystal may be made into an emulsion type product. The emulsion type product includes, but are not limited to, milky lotions and creams.

The examples of a cosmetically acceptable liquid oil, a polyhydric alcohol, a solid fatty alcohol and a surfactant, which can be used to form a liquid crystal, are as follows.

20 (1) Cosmetically acceptable liquid oil

The cosmetically acceptable liquid oil is included in said cosmetically acceptable carrier. The cosmetically acceptable liquid oil is in liquid form at room temperature. The cosmetically acceptable liquid oil can be liquid hydrocarbon oil, liquid natural oil, liquid fatty alcohol, liquid fatty acid, liquid fatty acid ester, liquid silicone oil, and paste wax and mixtures thereof.

25 Non-limiting examples of the liquid hydrocarbons are squalane, liquid mineral oil, and liquid polybutene.

Non-limiting examples of the liquid natural oil derived from plants useful in the present invention include almond oil, olive oil, sesame oil, safflower oil, avocado oil, cottonseed oil, jojoba oil, castor oil, soybean oil, palm kernel oil, coconut oil, and hydrogenated vegetable oil. Non-limiting examples of the liquid natural oil derived from animal sources useful in the present invention include mink oil and egg yolk oil.

35 Non-limiting examples of the liquid fatty alcohol useful in the present invention are isostearyl alcohol, lanolin alcohol, oleyl alcohol, hexadecyl alcohol, octyldodecanol alcohol, linoleyl alcohol, linolenyl alcohol, lauryl alcohol and arachidyl alcohol.

Fatty acid can be natural or synthetic, saturated, unsaturated, linear, or branched. Non-limiting examples of fatty acid useful in the present invention are caprylic, isostearic, linoleic, ricinoleic, and oleic acid.

Non-limiting examples of the liquid fatty acid ester useful in the present invention are  
5 cetyl octanoate, glyceryl trioctanoate, isopropyl linoleate, isopropyl myristate, isopropyl oleate, ethyl laurate, ethyl linoleate, octyl dodecyl myristate, octyl palmitate, octyl isopelargonate, octyl dodecyl lactate, isotridecyl isononanoate, oleyl oleate, isostearyl myristate, neopentyl glycol dioctanoate, and di(capryl/capric acid) propylene glycol and mixtures thereof. Other suitable  
10 esters include triglycerides such as caprylic triglycerides, capric triglyceride, isostearic triglyceride and adipic triglyceride.

Non-volatile, straight, and branched silicone oil such as dimethicone and phenyl dimethicone is also useful.

Other cosmetically acceptable liquid oil includes octyl methoxy cinnamate, cinoxate, and 2-ethylphexyl p-dimethaminobenzoate.

15 Either one kind or two or more kinds of the cosmetically acceptable liquid oil can be used in the present invention.

The cosmetically acceptable liquid oil can also act as an emollient, and can provide adhesion and durability properties to the cosmetic.

#### (2) Polyhydric alcohol

20 Polyhydric alcohol include glycerin, diglycerin, triglycerin, polyglycerin, polypropylene glycol, polyethylene glycol, ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, 1,4-butylene glycol, ethylene glycol monoalkyl ether, diethylene glycol monoalkyl ether, glucose, maltose, sucrose, lactose, xylitose, xylitol, sorbitol, mannitol, maltitol, malbit, panthenol, pentaerythritol, and hyaluronic  
25 acid and its salts.

Among the polyhydric alcohols, glycerin is preferred.

Either one kind or two or more kinds of the polyhydric alcohol can be used in the present invention.

#### (3) Solid fatty alcohol

30 Solid fatty alcohols include arachidyl alcohol, cetyl alcohol, stearyl alcohol, behenyl alcohol, myristyl alcohol, batyl alcohol, cholesterol and phytosterol.

Among the solid fatty alcohols, cetyl alcohol is preferred.

Either one kind or two or more kinds of the solid fatty alcohol can be used in the present invention.

#### -35 (4) Surfactant



Surfactants include nonionic surfactant and anionic surfactants.

Nonionic surfactants include alkanolamides such as coconut diethanolamide and lauramide DEA, block polymers such as block copolymer of propylene oxide and ethylene oxide, ethoxy fatty acids such as propyleneglycol monostearate, ethoxylated alcohols such as polyoxyethylene (20) stearyl ether, ethoxylated alkylphenols such as polyoxyethylene (10) nonylphenyl ether, ethoxylated fatty acids such as polyethyleneglycol (10 ethylene oxide) monostearate, ethoxylated fatty esters such as polyoxyethylene (5) glyceryl monostearate, ethoxylated fatty esters and oils such as polyoxyethylene (10) hydrogenated castor oil and polyoxyethylene (6) sorbitol beeswax, glycerol esters such as glyceryl monostearate and diglyceryl monostearate, lanolin-based derivatives such as polyoxyethylene lanolin, propoxylated and ethoxylated fatty acids, alcohols or alkyl phenols such as polyoxyethylene (10) polyoxypropylene (4) cetyl ether, protein-based surfactants such as polyoxyethylene (25) glycerin monopyroglutamic monoisostearate, solbitan derivatives such as sorbitan monostearate, polyoxyethylene (20) sorbitan monostearate and polyoxyethylene (60) sorbitol tetrastearate and sucrose and glucose esters and derivatives such as saccharose distearate and sucrose stearate.

Anionic surfactants include phosphate ester such as sodium polyoxyethylene (4) lauryl ether phosphate and DEA cetyl phosphate, phosphorous organic derivatives such as phosphated oleyl ether (10 ethylene oxide) and soaps such as sodium stearate and potassium cocoate.

Either one kind or two or more kinds of surfactant can be used in the present invention.

## E. Combination Actives

### (1) Sunscreens and Sunblocks

Regulation of skin darkening resulting from exposure to ultraviolet light can be achieved by using combinations of the active skin lightening agents together with sunscreens or sunblocks. Useful sunblocks include, for example, zinc oxide and titanium dioxide.

Ultraviolet light is a predominant cause of skin darkening. Thus, for purposes of skin lightening, the combination of the water-soluble reducing agent with a UVA and/or UVB sunscreen is desirable.

A wide variety of conventional suncreening agents are suitable for use in combination with the skin lightening agent. Segarín, et al., at Chapter VIII, pages 189 et seq., of Cosmetics Science and Technology, disclose numerous suitable agents. Specific suitable suncreening agents include, for example: p-aminobenzoic acid, its salts and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilates (i.e., o-aminobenzoates; methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, benzyl, menthyl, glyceryl, and dipropyleneglycol esters); Cinnamic acid derivatives (menthyl and benzyl esters, butyl cinnamoyl pyruvate); dihydroxycinnamic acid

derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxy-cinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); dihydroxy-naphthoic acid and its salts; o- and p-Hydroxybiphenyldisulfonates; coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl); diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, various aryl benzothiazoles); quinine salts (bisulfate, sulfate, chloride, oleate, and tannate); hydroxy- or methoxy-substituted benzophenones; uric and vilouric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carboto) (6-propyl piperonyl) ether; benzophenones (oxybenzene, sulisobenzene, dioxybenzene, benzoescorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzene; 4-isopropylidibenzoylmethane; butylmethoxydibenzoylmethane; etocrylene; and 4-isopropyl-di-benzoylmethane.

Of these, 2-ethylhexyl-p-methoxycinnamate, 4,4'-t-butyl methoxydibenzoyl-methane, 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid, digalloyltriolate, 2,2'-dihydroxy-4-methoxybenzophenone, ethyl-4-(bis(hydroxypropyl)) aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, 2-ethylhexylsalicylate, glyceryl-p-aminobenzoate, 3,3,5-trimethylcyclohexylsalicylate, methylanthranilate, p-dimethyl-aminobenzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethyl-amino-benzoate, 2-phenylbenzimidazole-5-sulfonic acid, 2-(p-dimethylaminophenyl)-5-sulfonicbenzoxazoic acid and mixtures of these compounds, are preferred.

More preferred sunscreens useful in the compositions useful in the present invention are 2-ethylhexyl-p-methoxycinnamate, butylmethoxydibenzoylmethane, 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid and mixtures thereof.

Also particularly useful in the compositions are sunscreens such as those disclosed in U.S. Patent No. 4,937,370 issued to Sabatelli on June 26, 1990, and U.S. Patent No. 4,999,186 issued to Sabatelli & Spirmak on March 12, 1991, both of which are incorporated herein by reference. The suncreening agents disclosed therein have, in a single molecule, two distinct chromophore moieties which exhibit different ultra-violet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range.

Preferred members of this class of suncreening agents are 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl) methylaminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-

5    -(2-ethylhexyl)methylaminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; and N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane and mixtures thereof.

10    A safe and effective amount of sunscreen may be used in the compositions useful in the present invention. The suncreening agent must be compatible with the water-soluble reducing agent. The composition preferably comprises from about 1% to about 20%, more preferably from about 2% to about 10%, of a sunscreening agent. Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF).

15    An agent may also be added to any of the compositions useful in the present invention to improve the skin substantivity of those compositions, particularly to enhance their resistance to being washed off by water, or rubbed off. A preferred agent which will provide this benefit is a copolymer of ethylene and acrylic acid. Compositions comprising this copolymer are disclosed in U.S. Patent 4,663,157, Brock, issued May 5, 1987, which is incorporated herein by reference.

(2) Anti-Inflammatory Agents

20    In a preferred skin lightening composition useful in the present invention, an anti-inflammatory agent is included as an active along with the water-soluble reducing agent. The inclusion of an anti-inflammatory agent enhances the skin lightening benefits of the compositions. The anti-inflammatory agent protects strongly in the UVA radiation range (though it also provides some UVB protection as well). The topical use of anti-inflammatory agents reduces darkening of the skin resulting from chronic exposure to UV radiation. (See U.S. Patent 4,847,071, Bissett, Bush, and Chatterjee, issued July 11, 1989, incorporated herein by reference; and U.S. Patent 4,847,069, Bissett and Chatterjee, issued July 11, 1989, incorporated herein by reference.)

25    A safe and effective amount of an anti-inflammatory agent may be added to the compositions useful in the present invention, preferably from about 0.1% to about 10%, more preferably from about 0.5% to about 5%, of the composition. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency.

30    Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionate, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate,

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fluosinolone acetonide, fluocinonide, fluocortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluormethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof may be used. The preferred  
 5 steroidal anti-inflammatory for use is hydrocortisone.

A second class of anti-inflammatory agents which is useful in the compositions includes the nonsteroidal anti-inflammatory agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc., of non-steroidal anti-inflammatory agents, reference may  
 15 be had to standard texts, including Antiinflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology, I, R. A. Scherrer, et al., Academic Press, New York (1974).

Specific non-steroidal anti-inflammatory agents useful in the composition invention include, but are not limited to:

- 20 i) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;
- ii) the salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal;
- 25 iii) the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepiract, clidanac, oxepinac, and felbinac;
- iv) the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;
- 30 v) the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tiroxaprofen, suprofen, alminoprofen, and tiaprofenic; and
- vi) the pyrazoles, such as phenybutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well  
 35 as the pharmaceutically-acceptable salts and esters of these agents. For example, etofenamate, a

flufenamic acid derivative, is particularly useful for topical application. Of the nonsteroidal anti-inflammatory agents, ibuprofen, naproxen, flufenamic acid, mefenamic acid, meclofenamic acid, piroxicam and felbinac are preferred; ibuprofen, naproxen, and flufenamic acid are most preferred.

5 Another class of anti-inflammatory agents which are useful in the compositions are the anti-inflammatory agents disclosed in U.S. Patent No. 4,708,966, Loomans et al., issued November 24, 1987. This patent discloses a class of nonsteroidal anti-inflammatory compounds which comprise specifically substituted phenyl compounds, especially substituted 2,6-di-  
10 tert-butyl phenol derivatives. For example, compounds selected from 4-(4'-pentyn-3'-one)-2,6-di-*t*-butylphenol; 4-(5'-hexynoyl)-2,6-di-*t*-butylphenol; 4-((S)-(-)-3'-methyl-5'-hexynoyl)-2,6-di-*t*-butylphenol; 4-((R)-(+)-3'-methyl-5'-hexynoyl)-2,6-di-*t*-butylphenol; and 4-(3',3'-dimethoxypropionyl)-2,6-di-*t*-butylphenol are useful in methods of the present invention; 4-(5'-hexynoyl)-2,6-di-*t*-butylphenol is most preferred.

15 Yet another class of anti-inflammatory agents which are useful in the compositions are those disclosed in U.S. Patent No. 4,912,248, Mueller, issued March 27, 1990. This patent discloses compounds and diastereomeric mixtures of specific 2-naphthyl- containing ester compounds, especially naproxen ester and naproxol ester compounds, having two or more chiral centers. For example, compounds selected from (S)-naproxen-(S)-2-butyl ester, (S)-naproxen-(R)-2-butylester, (S)-naproxol-(R)-2-methyl butyrate, (S)-naproxol-(S)-2-methyl  
20 butyrate, diastereomeric mixtures of (S)-naproxen-(S)-2-butyl ester and (S)-naproxen-(R)-2-butyl ester, and diastereomeric mixtures of (S)-naproxol-(R)-2-methyl butyrate and (S)-naproxol-(S)-2-methyl butyrate are useful in the present invention.

25 Finally, so-called "natural" anti-inflammatory agents are useful in methods of the present invention. For example, candelilla wax, alpha bisabolol, aloe vera, Manjistha (extracted from plants in the genus Rubia, particularly Rubia Cordifolia), and Guggal (extracted from plants in the genus Commiphora, particularly Commiphora Mukul), may be used.

Another preferred composition useful in the present invention comprises a skin lightening agent, a sunscreen, and an anti-inflammatory agent together for skin lightening in the amounts disclosed for each individually hereinabove.

### 30 (3) Anti-Oxidants/Radical Scavengers

In a preferred skin lightening composition useful in the present invention, an anti-oxidant/radical scavenger is included as an active along with the skin lightening agent. The inclusion of an anti-oxidant/radical scavenger increases the skin lightening benefits of the composition.

A safe and effective amount of an anti-oxidant/radical scavenger may be added to the compositions useful in the present invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition.

5 Anti-oxidants/radical scavengers such as ascorbic acid (vitamin C) and its salts, tocopherol (vitamin E), tocopherol sorbate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (commercially available under the tradename Trolox.), gallic acid and its alkyl esters, especially propyl gallate, uric acid and its salts and alkyl esters, sorbic acid and its salts, the ascorbyl esters of fatty acids, amines (e.g., N,N-diethylhydroxylamine, amino-guanidine), sulfhydryl compounds (e.g.,  
10 glutathione), and dihydroxy fumaric acid and its salts may be used.

In a preferred composition useful in the present invention, compositions comprise one, any two, or all three of a sunscreensing agent, anti-inflammatory agent, and/or an anti-oxidant/radical scavenging agent included as actives along with the skin lightening agent. The inclusion of two or all three of these agents with the skin lightening agent increases the skin  
15 lightening benefits of the composition.

#### (4) Chelators

In a preferred composition useful in the present invention, a chelating agent is included as an active along with the skin lightening agent. As used herein, "chelating agent" means an active agent capable of removing a metal ion from a system by forming a complex so that the  
20 metal ion cannot readily participate in or catalyze chemical reactions. The inclusion of a chelating agent increases the skin lightening benefits of the composition.

A safe and effective amount of a chelating agent may be added to the compositions useful in the present invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition. Chelators useful in compositions are disclosed in  
25 U.S. Patent Application Serial No. 619,805, Bissett, Bush & Chatterjee, filed November 27, 1990 (which is a continuation of U.S. Patent Application Serial No. 251,910, filed October 4, 1988); U.S. Patent Application Serial No. 514,892, Bush & Bissett, filed April 26, 1990; and U.S. Patent Application Serial No. 657,847, Bush, Bissett & Chatterjee, filed February 25, 1991; all incorporated herein by reference. Preferred chelators useful in compositions of the present  
30 invention are furildioxime and derivatives thereof.

In a preferred composition useful in the present invention, compositions comprise one, any two, any three, or all four of a sunscreensing agent, anti-inflammatory agent, anti-oxidant/radical scavenging agent, and/or chelating agent included as actives along with the skin  
35 lightening agent. The inclusion of two, three, or all four of these agents with the skin lightening agent increases the skin lightening benefits of the composition.

### (5) Retinoids

In a preferred composition useful in the present invention, a retinoid, preferably retinoic acid, is included as an active along with the skin lightening agent. The inclusion of a retinoid increases the skin lightening benefits of the composition. A safe and effective amount of a retinoid may be added to the compositions useful in the present invention, preferably from about 0.001% to about 2%, more preferably from about 0.01% to about 1% of the composition. As used herein, "retinoid" includes all natural and/or synthetic analogs of Vitamin A or retinol-like compounds which possess the biological activity of Vitamin A in the skin as well as the geometric isomers and stereo isomers of these compounds, such as all-trans retinoic acid and 13-cis-retinoic acid.

In a preferred composition useful in the present invention, compositions comprise one, any two, any three, any four, and/or all five of a sunscreensing agent, anti-inflammatory agent, anti-oxidant/radical scavenging agent, chelating agent, and/or a retinoid included as actives along with the skin lightening agent. The inclusion of two, three, four, or all five of these agents with the skin lightening agent increases the skin lightening benefits of the composition.

### (6) Other Optional Components

Other optional components include thickeners such as carboxy vinyl polymer, preservatives, liquid and paste pigments, astringents, pH buffers, perfumes, infrared screening agents, amphoteric and solid amorphous lipids, vitamins, nutrients, and skin conditioning agents.

Useful skin conditioning agents are beta-glycyrrhetic acid and its derivatives, vegetation extracts, allantoin, collagen, and extract and treated elastin fibers.

### F. Methods for Lightening Skin in Mammals

The present invention also relates to methods for skin lightening in mammals comprising topical application of the skin lightening composition of the present invention. The amount of active agent and frequency of application will vary widely depending upon the skin color already in existence in the subject, the rate of further darkening of the skin, and the level of lightening desired.

A safe and effective amount of skin lightening agent in a topical composition is applied, generally from about 1 mg to about 10 mg per cm<sup>2</sup> skin per application, preferably from about 2 mg to about 8 mg/cm<sup>2</sup> skin per application, more preferably from about 3 mg to about 7 mg/cm<sup>2</sup> skin, also preferably from about 4 mg to about 5 mg/cm<sup>2</sup> skin. Application preferably ranges from about four times a day to about twice a week, more preferably from about three times a day to about once every other day, more preferably still from about once daily to about twice daily. Application for at least five days is required to see a skin lightening effect in lower

animals. Application for at least one month is required to see an effect in humans. After lightening is achieved, the frequency and dosage can be reduced to a maintenance level, as desired. Such maintenance varies according to the individual, but is preferably from about 1/10 to about 1/2, more preferably from about 1/5 to about 1/3 of the original dosage and/or frequency, as needed.

A preferred method of the present invention for skin lightening in mammals involves applying the skin lightening composition of the present invention further comprising a safe and effective amount of one or more of a sunscreensing agent, an anti-inflammatory agent, an anti-oxidant/radical scavenging agent, a chelating agent and/or a retinoid. The amount of sunscreensing agent applied is preferably from about 0.01 mg to about 0.1 mg per cm<sup>2</sup> skin. The amount of anti-inflammatory agent applied is preferably from about 0.005 mg to about 0.5 mg, more preferably from about 0.01 mg to about 0.1 mg per cm<sup>2</sup> skin. The amount of anti-oxidant/radical scavenging agent preferably applied is from about 0.01 mg to about 1.0 mg, more preferably from about 0.05 mg to about 0.5 mg per cm<sup>2</sup> skin. The amount of chelating agent preferably applied is from about .001 mg to about 1.0 mg, more preferably from about 0.01 mg to about 0.5 mg, still more preferably from about 0.05 mg to about 0.1 mg per cm<sup>2</sup> skin. The amount of retinoid applied is preferably from about 0.001 mg to about 0.5 mg per cm<sup>2</sup> skin, more preferably from about 0.005 mg to about 0.1 mg per cm<sup>2</sup> skin. The amount of skin lightening agent applied is preferably from about 0.001 mg to about 2 mg per cm<sup>2</sup> skin per application, more preferably from about 0.01 mg to about 1 mg per cm<sup>2</sup> skin per application.

#### G. Procedure for making a skin lightening composition of the present invention

A skin lightening composition of the present invention can be made by a conventional method. However, if a skin lightening composition of the present invention comprises the liquid crystal, the composition can be made by the steps of

- (i) mixing a cosmetically acceptable liquid oil, a fatty alcohol, a surfactant and lecithin at the temperature of 60 °C to 100 °C to obtain mixture I, and
- (ii) mixing an water-soluble reducing agent, a polyhydric alcohol and water with the mixture I while maintained at the temperature of 45 °C to 100 °C.

The mixture obtained by the above steps (i) and (ii) is usually cooled to room temperature.

The other component can be mixed according to the conventional manner, however, generally oil-soluble components can be added in the above step (i) and water-soluble components can be added in the above step (ii).

The liquid crystal can be detected by observing the shape of the liquid crystal by a polarization microscope.



#### H. EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Composition No. 1 of the present invention is shown in Table 1.

Composition Nos. 2-5 of the present invention are shown in Table 2-5.

#### Procedure for making Composition No. 1

Caprylic/capric triglyceride (Migyo! 812), cetyl alcohol, polyoxyethylene (40) monostearate and lecithin are mixed together and heated to 70 °C. Then, sodium sulfite, sodium hydrogensulfite, deionized water and glycerin are added thereto with stirring and the mixture is emulsified. Then the emulsified mixture is cooled to room temperature with stirring to obtain an emulsion with a liquid crystal. The emulsion with the liquid crystal and all other ingredients than the above are mixed together to obtain Composition No. 1. The components of Composition No. 1 are shown in Table 1.

Table 1

Composition No. 1: Emulsion with liquid crystal

<u>Component</u>		<u>Amount (weight%)</u>
	Lecithin	3.00
5	Polyoxyethylene(40) monostearate (Myrj 52)	1.00
	Cetyl Alcohol	1.00
	Caprylic/Capric Triglyceride (Migyol 812)	15.00
10	D-delta Tocopherol	0.10
	Glycerin	5.00
	Propylparaben	0.10
	Methylparaben	0.20
	De-ionized Water	72.13
15	Sodium hydrogensulfite (manufactured by Nacalai tesque, INC.)	0.08
	Sodium Sulfite	0.20
	Sodium Hydroxide	0.59
	Carboxy vinyl polymer (Carbopol 980)	1.00
20	Benzyl Alcohol	0.60

Composition No. 1 shows a strong skin lightening activity.

Table 2

Composition No.2: Clear lotion with lecithin (No liquid crystal)

<u>Component</u>		<u>Amount (weight%)</u>
5	Denatured alcohol	5.000
	Polyoxyethylene(20) sorbitan monolaurate (Tween 20)	1.200
	Lecithin	0.020
	De-ionized water	87.160
10	Sodium hydrogensulfite (manufactured by Nacalai tesque, INC.)	0.100
	Sodium sulfite	0.200
	1,3-Butylene glycol	4.000
	Glycerin	2.000
15	EDTA-2Na	0.100
	Methylparaben	0.150
	Citric acid anhydrous	0.020
	Sodium citrate	0.050

20      Composition No.2 can be prepared, for example, by the following method.

1. Denatured alcohol, polyoxyethylene(20) sorbitan monolaurate (Tween 20) and lecithin, are mixed and dissolved at room temperature (25°C) to obtain mixture-1.

2. De-ionized water, sodium hydrogen sulfite, sodium sulfite, 1,3-butylene glycol, Glycerin, EDTA-2Na, methylparaben, citric acid anhydrous and sodium citrate are dissolved at room

25      temperature (25°C) to obtain mixture-2.

3. Mixture-1 and mixture-2 are mixed together to obtain composition No.2.

Table 3

Composition No.3: Milky lotion with lecithin (No liquid crystal)

<u>Component</u>		<u>Amount (weight%)</u>
	Decaglyceryl monostearate	1.200
5	Lecithin	0.500
	Cholesterol	0.050
	C10-30 Cholesterol/Lanosterol Esters	1.000
	Squalane	3.000
	Glyceryl trioctanoate	4.000
10	Propylparaben	0.050
	D-delta-Tocopherol	0.050
	De-ionized water	80.720
	Sodium hydrogensulfite	0.100
	(manufactured by Nacalai tesque, INC.)	
15	Sodium sulfite	0.300
	Carboxy vinyl polymer (Carbopol 941)	0.300
	1,3-Butylene glycol	6.000
	Glycerin	2.500
	Methylparaben	0.100
20	EDTA-2Na	0.050
	Sodium hydroxide	0.080

Composition No.3 can be prepared, for example, by the following method.

1. Decaglyceryl monostearate, lecithin, cholesterol, C10-30 cholesterol/lanosterol esters, squalane, glyceryl trioctanoate, propylparaben and D-delta-Tocopherol are mixed and dissolved at the temperature of 80°C to obtain mixture-1.
2. De-ionized water, sodium hydrogen sulfite, sodium sulfite, carboxy vinyl polymer (Carbopol 941), 1,3-butylene glycol, Glycerin, methylparaben, EDTA-2Na and sodium hydroxide are dissolved at the temperature of 80°C to obtain mixture-2.
3. Mixture-1 and mixture-2 are mixed together at the temperature of 80°C, then are cooled to room temperature(25°C) to obtain composition No.3.

Table 4

Composition No.4: Milky lotion with liquid crystal

<u>Component</u>		<u>Amount (weight%)</u>
	Polyoxyethylene (100) stearyl ether	0.500
5	Stearic acid	0.550
	Lecithin	0.800
	Cetyl alcohol	1.300
	Glyceryl monohydroxy stearate	0.750
	Cetyl palmitate	3.000
10	Petrolatum	2.000
	Liquid paraffin	2.000
	Octyldodecyl myristate	0.500
	Methyl polysiloxane (350CS)	0.300
	De-ionized water	84.200
15	Sodium hydrogensulfite	0.100
	(manufactured by Nacalai tesque, INC.)	
	Sodium sulfite	0.300
	Carboxy vinyl polymer (Carbopol 941)	0.050
	Acrylates/C10-30 alkyl acrylate crosspolymer	0.075
20	Glycerin	3.000
	Methylparaben	0.200
	Propylparaben	0.150
	EDTA-4Na	0.100
25	Potassium hydroxide	0.125

Composition No.4 can be prepared, for example, by the following method.

1. Polyoxyethylene (100) stearyl ether, stearic acid, lecithin, cetyl alcohol, glyceryl monohydroxy stearate, cetyl palmitate, petrolatum, liquid paraffin, octyldodecyl myristate and methyl polysiloxane (350CS) are mixed and dissolved at the temperature of 80°C to obtain mixture-1.
2. De-ionized water, sodium hydrogen sulfite, sodium sulfite, carboxy vinyl polymer (Carbopol 941), acrylates/C10-30 alkyl acrylate crosspolymer, glycerin, methylparaben, propylparaben, EDTA-4Na and potassium hydroxide are dissolved at the temperature of 80°C to obtain mixture-2.
3. Mixture-1 and mixture-2 are mixed together at the temperature of 80°C, then are cooled to room temperature (25°C) to obtain composition No.4.

Table 5

Composition No.5: cream with liquid crystal

<u>Component</u>		<u>Amount (weight%)</u>
	Stearic acid	0.250
5	PEG 100 stearate	0.250
	Lecithin	1.000
	Cethyl alcohol	1.800
	Stearyl alcohol	1.200
	Petrolatum	1.500
10	Liquid paraffin	2.000
	Isopropyl palmitate	1.000
	Methyl polysiloxane (350CS)	0.500
	De-ionized water	80.690
	Sodium hydrogensulfite	0.100
15	(manufactured by Nacalai tesque, INC.)	
	Sodium sulfite	0.300
	Carboxy vinyl polymer (Carbopol 934)	0.600
	Glycerin	8.000
	Methylparaben	0.250
20	Propylparaben	0.150
	EDTA-2Na	0.100
	Sodium hydroxide	0.310

Composition No.5 can be prepared, for example, by the following method.

- 25 1. Stearic acid, PEG 100 stearate, lecithin, cethyl alcohol, stearyl alcohol, petrolatum, liquid paraffin, isopropyl palmitate and methyl polysiloxane (350CS) are mixed and dissolved at the temperature of 80°C to obtain mixture-1.
2. De-ionized water, sodium hydrogen sulfite, sodium sulfite, carboxy vinyl polymer (Carbopol 934), Glycerin, methylparaben, propylparaben, EDTA-2Na and sodium hydroxide are dissolved
- 30 at the temperature of 80°C to obtain mixture-2.
3. Mixture-1 and mixture-2 are mixed together at the temperature of 80°C, then are cooled to room temperature(25°C) to obtain composition No.5.

The compositions of the present invention have strong skin lightening effect of mammalian skin compared versus compositions which comprise a hydroquinone derivative.

#### 35 Method example

This example sets forth a method for lightening mammalian skin using a composition of the present invention.

5 The composition of example No. 1 is applied 5 mg / cm<sup>2</sup> skin per application three times a day for one month. After one month, a strong skin lightening effect is seen. Once the desired level of the skin lightening is achieved, treatment is reduced to limit a day, to maintain the level of lightening.

10 It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to one skilled in the art and are to be included in the spirit and purview of this application and scope of the appended claims.

## WHAT IS CLAIMED IS:

1. A skin lightening cosmetic composition comprising;
  - a) a safe and effective amount of at least one water-soluble reducing agent selected from the group consisting of sodium sulfite, potassium sulfite, ammonium sulfite, sodium hydrogen sulfite, potassium hydrogen sulfite, ammonium hydrogen sulfite, sodium metabisulfite, potassium metabisulfite, formic acid oxalic acid and mixtures thereof; and,
  - b) a cosmetically acceptable carrierwherein the composition is substantially free of hydroquinone or its derivatives.
2. The skin lightening cosmetic composition of claim 1 comprising from about 0.1% to about 5% by weight of the composition, of the water-soluble reducing agent.
3. The skin lightening cosmetic composition of claim 1 further comprising lecithin.
4. The skin lightening cosmetic composition of claim 3 comprising from about 0.1% to about 5% by weight of the composition, of the water-soluble reducing agent.
5. The skin lightening cosmetic composition of claim 4 wherein the water-soluble reducing agent is selected from the group consisting of sodium sulfite, sodium hydrogen sulfite, sodium metabisulfite and mixtures thereof.
6. The skin lightening cosmetic composition of claim 1 comprising;
  - a) a safe and effective amount of at least one water-soluble reducing agent selected from the group consisting of sodium sulfite, potassium sulfite, ammonium sulfite, sodium hydrogen sulfite, potassium hydrogen sulfite, ammonium hydrogen sulfite, sodium metabisulfite, potassium metabisulfite, formic acid, oxalic acid and mixtures thereof;
  - b) a cosmetically acceptable liquid oil;
  - c) a polyhydric alcohol;
  - d) a solid fatty alcohol;
  - e) a surfactant;
  - f) water; and
  - g) lecithin



wherein the composition is substantially free of hydroquinone or its derivatives, and at least a portion of the above components (a), (b), (c), (d), (e), (f) and (g) forms a liquid crystal.

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7. The skin lightening cosmetic composition of claim 6 comprising ;

a) from about 0.1% to about 5% by weight of the composition, of the water-soluble reducing agent;

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b) from about 1% to about 50% of by weight of the composition, of the cosmetically acceptable liquid oil;

c) from about 0.1% to about 20% by weight of the composition, of the polyhydric alcohol;

d) from about 0.1% to about 20% by weight of the composition, of the solid fatty alcohol;

e) from about 0.1% to about 10% by weight of the composition, of the surfactant;

10

f) from about 40% to about 90% by weight of the composition, of water; and

g) from about 0.01% to about 10% by weight of the composition, of lecithin.

8. The skin lightening cosmetic composition of claim 7 wherein said reducing agent is selected from the group consisting of sodium sulfite, sodium hydrogen sulfite, sodium metabisulfite and mixtures thereof.

9. The skin lightening cosmetic composition of claim 7 wherein the cosmetically acceptable liquid oil is a triglyceride.

10. The skin lightening cosmetic composition of claim 7 wherein the cosmetically acceptable liquid oil is caprylic/capric triglyceride.

11. The skin lightening cosmetic composition of claim 7 wherein the polyhydric alcohol is glycerin.

12. The skin lightening cosmetic composition of claim 7 wherein the solid fatty alcohol is cetyl alcohol.

13. The skin lightening cosmetic composition of claim 7 wherein the composition is an emulsion.

14. The method for skin lightening in mammals comprising topically applying to the skin the skin lightening cosmetic composition of claim 2.
15. The method of claim 14 comprising topically applying to the skin the skin lightening cosmetic composition of claim 8.
16. A process for preparing a skin lightening cosmetic composition which comprises the steps of
- 5 (i) mixing
- (a) a cosmetically acceptable liquid oil
- (b) a solid fatty alcohol
- (c) a surfactant, and
- (d) lecithin
- at the temperature of 60 °C to 100 °C to obtain mixture 1, and
- (ii) mixing with the mixture 1
- 10 (e) an water-soluble reducing agent
- (f) a polyhydric alcohol, and
- (g) water
- while maintained at the temperature of 45 °C to 100 °C;
- wherein the composition is substantially free of hydroquinone or its derivatives, and at
- 15 least a portion of the above components (a), (b), (c), (d), (e), (f) and (g) forms a liquid crystal.

# INTERNATIONAL SEARCH REPORT

Intern. Application No.  
PCT/US 96/17522

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 847 075 A (TAKAHASHI) 11 July 1989 see claims 1,2; example 3 ---	1-16
A	STN, File Supplier, Karlsruhe, DE, File XP002053265 Chemical Abstracts, vol 122, AN=16874 see the abstract ---	1-16
A	EP 0 419 901 A (SANSHO SEIYAKU) 3 April 1991 see the whole document ---	1-16
A	FR 2 088 848 A (PLANCHARD) 7 January 1972 see the whole document ---	1-16

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

26 January 1998

Date of mailing of the international search report

12.02.98

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## INTERNATIONAL SEARCH REPORT

Internat'l Application No.

PCT/US 96/17522

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No. .
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A	STN, File Supplier, Karlsruhe, DE, File XP002032939 Chemical Abstracts, vol 109, an=176106 see the abstract ---	1-16
A	EP 0 404 162 A (SANSHO SEIYAKU) 27 December 1990 see the whole document ---	1-16
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Information on patent family members

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PCT/US 96/17522

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